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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,078	07/10/2003	Steven P. Schwendeman	22727/04125	3384

24024 7590 09/01/2010

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
09/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/617,078	SCHWENDEMAN ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 27-62* is/are pending in the application.

4a) Of the above claim(s) *27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 30-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response filed on 8 June 2010 has been acknowledged and duly made of record.

Upon further consideration, applicants' arguments are found persuasive in as far as the sole Sokoll *et al.* (WO 98/28357) reference does not fairly anticipate each and every limitation of the alleged invention.

Applicant's arguments, see page 8, filed 8 June 2010, with respect to the 35 U.S.C. § 102(b) have been fully considered and are persuasive. The Claim Rejection - 35 U.S.C. § 102(b) of 8 June 2010 has been withdrawn.

Status of the Claims

Claims 1-6 and 30-62 are pending further prosecution on the merits. Claims 27-29 are withdrawn from further consideration. Claims 7-26 are cancelled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 30-31, 38-41, and 47-50 (in as far as claims 1-6, 30-31, 38-41, and 47-50 teach [that] one or more antigens are encapsulated in the microparticles rejected under 35 U.S.C. 102(b) as being anticipated by Schwendeman et al.

Schwendeman et al. teach in the instant abstract [m]ethods for reducing or inhibiting the irreversible inactivation of water-soluble biologically active agents in **biodegradable polymeric delivery systems** which are designed to release such agents over a prolonged period of time, such as PLGA delivery systems are provided. The method comprises preparing a PLGA delivery systems whose microclimate, i.e. the pores where the active agent resides, uniformly or homogenously maintain a pH of between 3 and 9, preferably between 4 and 8, more preferably between 5 and 7.5 during biodegradation. Depending on the size of the delivery system, and the initial bulk permeability of the polymer, this result is achieved by (a) incorporating a water-soluble carrier into the delivery system, (b) incorporating **a select basic additive (or antacid)** into the delivery system, (c) incorporating both a water soluble carrier and a select basic additive into the delivery system, (d) adding a pore forming molecule for increasing the rate of release of low molecular weight monomers and oligomers into the delivery system, (e) using A PLGA polymer with reduced glycolide content, i.e. PLGA with from 100% to 75% lactide and 0 to 25% glycolide) (f) using a **microencapsulation** method that yields a more extensive pore-network, e.g. oil-in-oil emulsion-solvent extraction as opposed to water-in-oil-in water-solvent evaporation method, and (g) combinations thereof.

Based upon part (e) in the foregoing drawn to PLGA and glycolide, claims 49, 50, and 60 anticipate the claimed invention in view of Schwendeman et al. teaching ranges that are encompassed by the said ranges of the claimed invention.

Schwendeman et al. teach in column 5 at lines Particles prepared as described above are useful for delivering or targeting drugs, diagnostic agents, vaccines and genes to the circulation

or specific sites of a mammalian body. This embodiment fully anticipates the limitations in the alleged invention drawn to enhancing an immunogenic response in a mammalian subject.

Schwendeman et al. teach in paragraph 9 in lines 1-12 [that] [t]he present invention provides methods of preparing PLGA delivery systems which stabilize the soluble biologically active agents that are encapsulated therein. As used herein, the term stabilize refers to an improvement in the stability of the encapsulated agent, which is necessary to approach or achieve a stable state. **A stable biologically active agent as used herein refers to a biologically active agent such as a protein, peptide, oligonucleotide, low-molecular weight drug, or vaccine antigen that retains at least 80%, preferably 90%, of its original structure and/or biological activity during its release from the PLGA delivery system**.

The limitation of claims 4 and 39 which is drawn to a well-established properties of a basic additive holds no patentable weight in light of the fact that a basic additive such as an antacid would be expected to have a pH of a saturated solution at 37°C in the range from about 6.8 to about 12.5 and a solubility in water at 37°C from 1.2×10^{-2} to about 3×10^{-11}.

Schwendeman et al. teach in paragraph 13 [that] [s]uitable basic additives are magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, zinc carbonate, zinc hydroxide, zinc phosphate, aluminum hydroxide, basic aluminum carbonate, dihyroxyaluminum sodium carbonate, dihydroxyaluminum aminoacetate, ammonium phosphate, calcium phosphate, calcium hydroxide, magaldrate. Preferably, the polymer comprises from 50% to 100% lactide or lactic acid, which may be a D isomer, L-isomer, or a D-,L-racemic mixture, and from 50% to 0% of a glycolide or glycolic acid. The polymer has an inherent viscosity of from 0.1 to 2.0 dl/g.

Thus, claims 5, 40, and 53 anticipate the claimed invention in view of the paragraph immediately *supra*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 30-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwendeman et al. (USPGPUB 2002/0009493 A1), Elahi (USPN 4,280,816), Wright et al. (USPN 6,379,704 B2), Thanavala et al. (Affinity, cross-reactivity and biological effectiveness of rabbit antibodies against a synthetic 37 amino acid C-terminal peptide of human chorionic gonadotropin, Clin exp. Immunol. (1980) 39, 112-118 in view of Setterstrom et al. (USPN 6, 309,669 B1).

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Schwendeman et al. teach in the instant abstract [m]ethods for reducing or inhibiting the irreversible inactivation of water-soluble biologically active agents in **biodegradable polymeric delivery systems** which are designed to release such agents over a prolonged period of time, such as PLGA delivery systems are provided. The method comprises preparing a PLGA delivery systems whose microclimate, i.e. the pores where the active agent resides, uniformly or homogenously maintain a pH of between 3 and 9, preferably between 4 and 8, more preferably between 5 and 7.5 during biodegradation. Depending on the size of the delivery system, and the initial bulk permeability of the polymer, this result is achieved by (a) incorporating a water-soluble carrier into the delivery system, (b) incorporating **a select basic additive (or antacid)** into the delivery system, (c) incorporating both a water soluble carrier and a select basic additive into the delivery system, (d) adding a pore forming molecule for increasing the rate of release of low molecular weight monomers and oligomers into the delivery system, (e) using A PLGA polymer with reduced glycolide content, i.e. PLGA with from 100% to 75% lactide and 0 to 25%

glycolide) (f) using a **microencapsulation** method that yields a more extensive pore-network, e.g. oil-in-oil emulsion-solvent extraction as opposed to water-in-oil-in water-solvent evaporation method, and (g) combinations thereof.

Based upon part (e) in the foregoing drawn to PLGA and glycolide, claims 49, 50, and 60 are made obvious in view of Schwendeman et al. teaching ranges that are encompassed by the said ranges of the claimed invention.

Schwendeman et al. teach in column 5 at lines Particles prepared as described above are useful for delivering or targeting drugs, diagnostic agents, vaccines and genes to the circulation or specific sites of a mammalian body. This embodiment fully makes obvious the limitations in the alleged invention drawn to enhancing an immunogenic response in a mammalian subject.

Schwendeman et al. teach in paragraph 9 in lines 1-12 [that] The present invention provides methods of preparing PLGA delivery systems which stabilize the soluble biologically active agents that are encapsulated therein. As used herein, the term stabilize refers to an improvement in the stability of the encapsulated agent, which is necessary to approach or achieve a stable state. **A stable biologically active agent as used herein refers to a biologically active agent such as a protein, peptide, oligonucleotide, low-molecular weight drug, or vaccine antigen that retains at least 80%, preferably 90%, of its original structure and/or biological activity during its release from the PLGA delivery system**.

The limitation of claims 4 and 39 which is drawn to a well-established properties of a basic additive holds no patentable weight in light of the fact that a basic additive such as an

antacid would be expected to have a pH of a saturated solution at 37°C in the range from about 6.8 to about 12.5 and a solubility in water at 37°C from 1.2×10^{-2} to about 3×10^{-11}.

Schwendeman et al. teach in paragraph 13 [that] [s]uitable basic additives are magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, zinc carbonate, zinc hydroxide, zinc phosphate, aluminum hydroxide, basic aluminum carbonate, dihyroxyaluminum sodium carbonate, dihydroxyaluminum aminoacetate, ammonium phosphate, calcium phosphate, calcium hydroxide, magaldrate. Preferably, the polymer comprises from 50% to 100% lactide or lactic acid, which may be a D isomer, L-isomer, or a D-,L-racemic mixture, and from 50% to 0% of a glycolide or glycolic acid. The polymer has an inherent viscosity of from 0.1 to 2.0 dl/g.

Thus, claims 5, 40, and 53 are made obvious in view of the paragraph immediately *supra*.

Elahi et al. teach a process for the immunoassay of antigens in a biological sample wherein an element comprised of particulate supported antibody loosely encapsulated and confined within a porous filter membrane material is utilized for addition to the biological sample. The method is particularly applicable to the radioimmunoassay (RIA) and enzyme-linked immunoassay (ELIA) techniques for determining the presence and concentration of minute amounts of protein antigens in biological fluid samples, and for performing multiple assays utilizing these methods.

The process according to this invention may be practiced in a number of ways. Thus, for example, in one embodiment, antibody can be complexed (e.g., sorbed) onto the particulate solid support material, the particulates then loosely encapsulated in the rigid porous filter membrane, and the capsule element added to a biological sample containing labelled antigen. Alternatively,

the particulate solid support material may have complexed thereon both the antibody and its labelled antigen prior to encapsulation and addition to a biological fluid.

For IgG, the conjugation between the enzyme, alkaline phosphatase and the IgG antigen is made by glutardialdehyde. 0.1 ml of a clear suspension of the enzyme solution is added to 0.1 ml of a solution containing 0.5 mg pure rabbit IgG. The mixture has a IgG-alkaline phosphatase ratio of 1:3 and dialyzed overnight against phosphate buffered saline. The contents are then reacted with 10 ul of 4.2% glutardialdehyde in phosphate buffered saline for 2 hours. The mixture is diluted to 1 ml with buffered saline, dialyzed overnight and separated on a Spharose 6B column in 0.05 M Tris-HCL buffer (pH 8.0). The eluted enzyme-labelled antigen is stabilized with 5% human serum albumin and stored at 4.degree. C. with 0.2% NaN.sub.3.

Wright et al. teach a method for preparing microparticles having a selected polymer molecular weight. The hold time and temperature of a solution containing a nucleophilic compound and a polymer having a starting molecular weight are controlled in order to control the molecular weight of the polymer in the finished microparticle product. In this manner, a selected polymer molecular weight in the finished microparticle product can be achieved from a variety of starting material molecular weights (abstract only).

Wright et al teach administration of compound to a human subject (patient) (column 27, line 50).

Wright et al teach polymeric excipients (column 1, lines 48-67).

Wright et al. teach lactide: glycolide ratios with a disclosure of 100:0 (column 9, line 24)

Wright et al. teach PLGA 50:50 (column 12, line 52).

Wright does not teach human chorionic gonadotropin (hCG) or carboxyl terminal peptides.

However, Thanavala et al. does teach embodiments drawn to methods wherein the (hCG) antigen is a carboxyl terminal peptide of the beta subunit of (hCG) (Summary, page 112 and page 113, 2nd paragraph). Accordingly, Thanavala et al. teach antibodies with (hCG) were raised by immunizing rabbits with a synthetic peptide (see Summary. Page 112). Further, Thanavala specifically teach agglutination via a preparation of a (hCG) coated latex particles showed positive agglutination by day and were strongly positive by day 15 after immunization. Thus, it would be apparent to the skilled artisan that conjugation (i.e., covalent and/or ionic agglutination) is supported by the Thanavala et al. reference above.

Wright et al. and Thanavala et al. do not teach adjuvants.

However, Setterstrom et al teach adjuvants. Novel burst-free, sustained release biocompatible and biodegradable microcapsules, which can be programmed to release their active core for variable durations ranging from 1-100 days in an aqueous physiological environment. The microcapsules are comprised of a core of polypeptide or other biologically active agent encapsulated in a matrix of poly (lactide/glycolide) copolymer, which may contain a pharmaceutically-acceptable adjuvant as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99 (abstract only).

Additionally, Setterstrom et al. teach administration to mammals (column 27, line 50).

Thus, it would have been *prima facie* obvious to combine and/or interchange the microparticles of a biodegradable polymer to the mammalian subject as taught by Schwendeman et al. with the particulates as taught by Elahi et al. and Wright. Further, the antigens as taught by

Schwendeman et al. are further made obvious via Thanavala et al. teaching an hCG antigen. Thus, the hCG antigen of Thanavala would be obvious to be included with the antigens as taught by Schwendeman et al. The adjuvants/excipients as taught by Setterstrom et al. are reasonably combinable with the microparticles of Schwendeman et al., Elahi et al., Wright and Thanavala.

Furthermore, it would have *prima facie* obvious to combine or incorporate together the teachings of Wright et al. with the teachings of Thanavala et al. Wright et al. teaches the objective and/or subject matter disclosed within instant claims which are directed to methods for preparing microparticles having a selected polymer molecular weight. Thanavala et al. provide the motivation to combine based on the disclosure directed to methods wherein the (hCG) antigen is a carboxyl terminal peptide of the beta subunit of (hCG). Wright et al. in turn discloses such microparticle formulations comprising examples of suitable biologically active agents including antigens. Setterstrom et al. further provides motivation by disclosing the general use of adjuvants in preparations of microparticles. Based on the explanation above, the skilled artisan would at once recognize the subject matter of Wright as being complementary with the limitations of Thanavala in regard to the mention of specific antigen types. Setterstrom et al. accordingly provides further evidence of the inclusion of variable and suitable biologically active agents, i.e., excipients and adjuvants.

The instant claims are made obvious by the combined teachings of Wright et al, Thanavala et al. and Setterstrom et al.

Absent evidence to the contrary, the disclosed antigens encapsulated within the microparticles may also be interpreted based on the representation of the claims to be also

conjugated to the microparticles which is conventionally defined as being *connected, linked, and/or attached.*

Instant claims 42-45 and 54-56 are drawn to characterization optimizations of magnitudes of ratio combinations of the basic additive in relation to the antigen of which it is coupled with in claimed invention. Similarly, the basic additive is compared in ratio strength to the biodegradeable polymer of which it is encapsulated. The skilled artisan would at once recognize the process of such optimizations of ratio magnitudes as a part of due and routine experimentation. Thus, instant claims 42-45 and 54-56 are made obvious due to the common practice in pharmacy technology to generate therapeutic ranges via extensive and routine experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY E. BETTON whose telephone number is (571)272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627